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Effects of interval-load versus constant-load training on the BODE index in COPD patients

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Summary
The BODE index is frequently used to assess functional capacity in patients with COPD. The aim of this study was to investigate the effectiveness of interval-load training (ILT) to improve the BODE index in comparison to the commonly implemented constant-load training (CLT).

Forty-two patients with COPD [FEV_1: (mean ± SEM) 42 ± 3% predicted] were randomly allocated to either ILT ($n = 21$) or CLT ($n = 21$). The training program consisted of cycling exercise 3 days/week for 10 weeks. Patients assigned to ILT exercised at a mean intensity of 126 ± 4% of baseline peak work rate (Wpeak) with 30-s work periods alternated with 30-s rest periods for 45 min per day, whereas patients allocated to CLT exercised at a mean intensity of 76 ± 5% of baseline Wpeak for 30 min per day. The BODE index and its components: body mass index, FEV_1, MMRC dyspnea score and the 6-min walk test (6-MWT) as well as cycling Wpeak were assessed before and after both exercise training regimes.

Both ILT and CLT significantly ($p < 0.001$) decreased the BODE index (from 4.8 ± 0.5 to 4.0 ± 0.5 units and from 4.4 ± 0.5 to 3.8 ± 0.5 units, respectively). In addition, both ILT and CLT significantly decreased the MMRC dyspnea score by 0.4 ± 0.1 units and increased the 6-MWT (by 52 ± 16 and 44 ± 12 m, respectively) as well as cycling Wpeak (by 14 ± 2 and 10 ± 2 W, respectively). The magnitude of these changes was not significantly different between ILT and CLT. Consequently, ILT is equally effective to CLT in terms of improving the BODE index in patients with COPD and as such it may constitute an alternative rehabilitative modality in COPD.

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Introduction

Pulmonary rehabilitation is a multidisciplinary process of care for patients with Chronic Obstructive Pulmonary Disease (COPD) that is tailored and designed to optimize physical and social performance and autonomy.[1] Exercise training is widely accepted as the cornerstone for enhancing the functional ability and the quality of life in patients with COPD.[2,3]

The BODE index is a simple multidimensional grading index which incorporates measurement of the body mass index (BMI), the forced expiratory volume in one second (FEV_1), the Modified Medical Research Council dyspnea scale (MMRC) and the 6-min walk test (6-MWT). The BODE index is usually used to assess functional capacity and prognosis of mortality in patients with COPD.[4,5] In particular, two of the outcomes of the BODE index, the 6-MWT and the MMRC dyspnea scale are routinely used in patients with COPD to assess changes in functional capacity following implementation of pulmonary rehabilitation and also the severity of perceived respiratory disability of daily activities, respectively.[6–8]

The majority of rehabilitation programs typically implement constant-load training for 30–40 min, three to five times per week.[9] The intensity of training is recommended to be higher than 60% of peak workload (Wpeak) in order to obtain physiological adaptations.[10–13] However, patients with severe airflow limitation cannot tolerate such prolonged periods of constant-load training at high intensity levels.[12] In these patients, interval-load training, consisting of repeated periods of maximal or high intensity exercise alternating with short intervals of rest or low intensity exercise levels, constitutes a good alternative training strategy to constant-load training.[14–16]

In healthy subjects interval-load training leads to a training effect that is similar to that of constant-load training but with lower blood lactate concentration during the actual training sessions.[17,18] Similarly, in patients with moderate to severe COPD, interval-load training consisting of maximal exercise intensity for 30-s alternating with 30-s rest periods, has been shown to be equally effective to constant-load training sustained at 65–80% of Wpeak in terms of enhancing cycle ergometry exercise tolerance and peak oxygen consumption.[14] Importantly, interval-load training is associated with lower levels of dyspnea and leg discomfort during the training sessions.[14,19] However, to the best of our knowledge no trials have been conducted to investigate whether interval-load training is equally effective to constant-load training in terms of increasing functional capacity in patients with COPD as this is assessed by the BODE index and its components.

Therefore, the aim of this study was to compare the effect of interval-load training to constant-load training in terms of improving the BODE index and its components in patients with COPD. Based on the findings of previous studies[19,20] showing similar effects of the two training modalities on the magnitude of adaptations in peripheral muscle fiber cross-sectional area, oxidative capacity and capillarity and also on the degrees of improvement in exercise tolerance and peak oxygen consumption, it was hypothesized that the improvement in the BODE index and its components would not differ between interval- and constant-load training.

Methods

Study design

Forty-two COPD patients with GOLD stages II, III and IV[21] admitted to a comprehensive pulmonary rehabilitation program. Inclusion criteria required patients to be younger than 75 years old with a $FEV_1 \leq 80\%$ predicted without significantly reversibility (<12% change of initial FEV_1 values after bronchodilator), clinical stable with no significant co-existing disease that affects the patients ability to undertake exercise training. The study was approved by the institution's Ethics Committee. The aim of the study was fully explained to the patients and a written informed consent was obtained from all participants.

Before and after a 10-week period of pulmonary rehabilitation patients were asked to record their perceived breathlessness on the MMRC scale. In addition, each patient undertook a 6-MWT, an incremental cycle ergometry test to assess Wpeak and pulmonary function assessment tests. Immediately, after the baseline assessment patients were randomly assigned into two different training modalities: interval-load training (ILT) and constant-load training (CLT). Based on the findings of our previous studies[14,19,20] randomization was stratified according to the patients' baseline lung function (FEV_1% predicted lower or higher than 50) and cycling exercise Wpeak (higher or lower than 50 W).

Pulmonary function assessment

Spirometry for the determination of FEV_1 and FVC was performed with the patient in the sitting position using a Spirometer (Master Jaeger, Germany) according to recommended techniques.[22] Maximal voluntary ventilation (MVV) was estimated indirectly by multiplying FEV_1 by 40.[23]

Arterial tensions of O_2 (PaO_2) and CO_2 ($PaCO_2$), and pH were measured from 2 mL blood samples using a blood gas electrode system combined with a co-oximeter (ABL625, radiometer, Copenhagen, Denmark) within 10 min of collection.

Incremental exercise tests

An incremental exercise protocol on a cycle ergometer was performed by each patient in order to assess Wpeak. The work rate increments were determined according to the equations reported by Wasserman et al.[23] The protocol of the incremental exercise test was as follows: after 3-min of rest and 3-min of unloaded pedaling, the work rate was increased by 5–10 W every 1-min to the limit of tolerance. During each test cardiac frequency (f_c) was recorded by an ECG (Marquette Max, HELLIGE GMBH, Germany) and percentage O_2 saturation (%SpO_2) by a portable pulse oximeter (Nonin 8600 Nonin medical, Plymouth, USA). Also the modified Borg scale[24] was used to rate the magnitude of perceived dyspnea and leg discomfort every 2-min throughout the test and at the cessation of exercise.

6-min walking tests

The 6-MWT was performed according to the instructions of the American Thoracic Society, i.e.: the maximum distance walked by each patient on an 18-meter hospital corridor in 6 min was assessed.[7] Each patient performed the test twice on two consequent days. Patients were instructed to walk from end to end, at their own pace, while attempting to cover as much distance as possible in the allotted 6-min time. Intensity of dyspnea and leg discomfort were assessed by the modified Borg scale,[24] whereas f_c, and $\%SpO_2$ were recorded every min and at the end of 6-MWT. In those patients in whom O_2 saturation fell below 88% during the test O_2 was supplemented at a rate of 1.5–2.0 L/min.

MMRC dyspnea scale

Patients were asked to rate their perceived breathlessness on the modified MRC scale consisting of 5 points.[8]

BODE index

We recorded the BODE index for each patient by recording his/her body mass index (BMI), the forced expiratory volume in one second (FEV_1), the MMRC score, and the 6-MWT before and after the pulmonary rehabilitation program.[4,5]

Intervention protocols

The pulmonary rehabilitation program involved supervised exercise training on electromagnetically braked cycle ergometers (Cateye Ergociser, ECI600; Osaka Japan). The patients assigned to CLT ($n = 21$) exercised for 30-min at an intensity that was initially equivalent to 60% Wpeak, whereas patients assigned to ILT ($n = 21$) trained for 40-min by alternating 30-s exercise intervals initially at 100% Wpeak with 30-s rest periods as previously described.[14,19,20] Total workload was increased on a weekly basis for each training group. During each training session dyspnea sensations and leg discomfort were recorded on the modified Borg scale, whereas f_c and $\%SpO_2$ were continuously monitored. All patients were provided with dietary advice by a dietician and instructions on breathing control techniques by physical therapists. Oxygen was supplemented during training to all patients at a rate of 1.5–2.0 L/min.

Statistical analysis

The minimum sample size was calculated based on 80% power and a two-sided 0.05 significance level using the Statistica 7.0 statistical program. Sample size capable of detecting a change of −0.9 for the BODE index was estimated using data obtained from a previous study by Celli et al.[4] using a standard deviation of 0.3. The critical sample size was estimated to be 17 patients per training group. Data are presented as mean ± standard error of mean (SEM). Two-way analysis of variance (ANOVA) with repeated measures was used to compare the pre- and post-rehabilitation changes in the 6-MWT, the Wpeak, the 6-MWT and the BODE index between groups. When ANOVA detected significant changes, post-hoc comparisons by the Scheffer test were performed for multiple significant differences. The level of statistical significance was at $p < 0.05$.

Results

The patients' baseline characteristics for each training group are shown in Table 1. The number of patients assigned to each of the three GOLD stages did not differ between ILT and CLT. None of the lung function characteristics were different between groups. At baseline the 6-MWT, the Wpeak and the BODE index did not show statistically significant differences between the two groups (Table 1).

Training intensity and symptoms

Mean training intensity sustained during CLT and ILT was 76 ± 5% and 126 ± 4% Wpeak, respectively, whereas total training workload was not different between groups. However, the magnitude of dyspnea sensations and leg discomfort was significantly ($p < 0.001$) lower in the ILT group compared to the CLT group (dyspnea: 3.0 ± 0.4 versus 3.5 ± 0.4, respectively) and (leg discomfort: 2.9 ± 0.5 versus 3.5 ± 0.5, respectively), (Fig. 1).

Table 1 Baseline characteristics of the study population.

Training group	Constant-load training ($n = 21$)	Interval-load training ($n = 21$)
Male/Female	16/5	17/4
Age (yrs)	66 ± 3	65 ± 3
Weight ((kg)	67 ± 4	69 ± 3
Height (cm)	165 ± 2	164 ± 2
GOLD stage (II, III, IV)	7/8/6	7/7/7
BMI ($kg\ m^{-2}$)	24.6 ± 0.7	25.5 ± 0.8
FEV_1 (L)	1.13 ± 0.1	1.07 ± 0.1
FEV_1 (% pred)	44.2 ± 4.2	40.1 ± 3.9
FVC (L)	2.8 ± 0.2	2.6 ± 0.2
FVC (% pred)	83.0 ± 5.5	74.5 ± 4.9
MVV ($L\ min^{-2}$)	44.5 ± 4.2	42.1 ± 4.1
PaO_2 (mmHg)	66.0 ± 2.6	69.1 ± 1.6
$PaCO_2$ (mmHg)	39.6 ± 1.1	39.9 ± 0.7
pH	7.35 ± 0.01	7.41 ± 0.01
Wpeak (W)	51 ± 4	48 ± 4
Wpeak (% pred)	39 ± 4	39 ± 4
Peak SpO_2 (%)	93 ± 1	94 ± 1
6-MWT (m)	330 ± 20	333 ± 23
MMRC	2.7 ± 0.2	3.1 ± 0.2[a]
BODE index score	4.4 ± 0.5	4.8 ± 0.5

Data are presented as mean ± SEM. BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MVV: maximal voluntary ventilation (estimated as $FEV_1 \times 40$); peak SpO_2 (%): percentage oxygen saturation; 6-MWT: 6-min walking test; Wpeak: peak workload; Wpeak (% pred): predicted % peak workload; MMRC: Modified Medical Research Council dyspnea scale, BODE index score.

[a] Significant difference between groups at $p < 0.01$.

Cycle ergometry exercise tests

Following the two training regimes both groups achieved significant ($p < 0.001$) improvements in Wpeak [ILT by 14 ± 2 W and CLT by 10 ± 2 W (Table 2)]. The magnitude of change did not differ between groups.

BODE index

The mean change in the BODE index was for ILT 0.8 ± 0.1 units ($p < 0.001$) and for CLT 0.6 ± 0.1 units ($p < 0.02$) (Fig. 2).

Fig. 3, (A) CLT and (B) ILT training group displays the percentage distribution of patients relative to the changes in units of the BODE index. The percentage of patients reduced the BODE index by 1.0 unit was twice as high for the ILT (B) compared to the CLT group (A). Improvement in the BODE index is demonstrated by decreases in the index, while an increase in value implies worsening in the BODE index.

BODE index components

Neither BMI nor FEV_1% predicted changed after the two training regimes (Table 2).

The MMRC dyspnea scale values were significantly different between CLT and ILT group at baselines and at the end of the pulmonary rehabilitation programs (Tables 1 and 2). Following training, both CLT and ILT groups significantly improved the MMRC scale by 0.4 ± 0.01 points ($p < 0.01$), (Table 2).

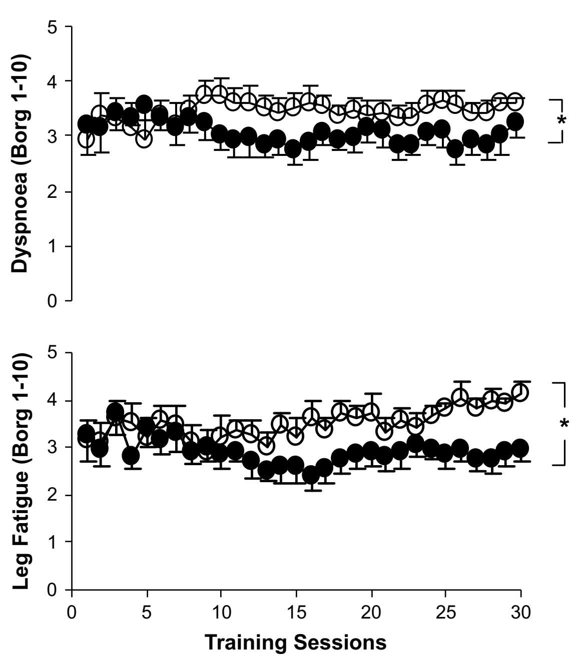

Figure 1 Sensations of dyspnea (top) and leg discomfort (bottom) during the rehabilitative training sessions between the constant-load training group (open circle) and the interval-load training group (closed circle). Asterisks denote significant differences ($p < 0.001$) between training groups.

6-min walking test

According to the ATS guidelines for the execution of the 6-MWT[7] each patient performed two tests before and after the pulmonary rehabilitation programs. The analysis of the data revealed that the distance covered during the second trial was significantly greater than the first one by $7 \pm 2\%$ ($p < 0.01$).

Post-rehabilitation analysis of changes in walking distance showed that the CLT group improved the 6-MWT significantly ($p < 0.001$) by 44 ± 12 m and the ILT group by 52 ± 16 m ($p < 0.001$) (Fig. 4). The magnitude of improvement did not differ significantly between the two groups (Table 2). Following completion of the program, dyspnea sensation and leg discomfort recorded at the end of the 6-MWT did not change significantly in either of the training regimes (Table 2).

Discussion

The main finding of this study is that in patients with COPD interval-load training is equally effective to constant-load training in terms of inducing a significant improvement in the BODE index score as well as in the 6-min walking distance and the MMRC dyspnea scale.

Interval-load training has been implemented in the studies by Vogiatzis et al.[14,19,20] as an alternative and equally effective training method to the constant-load exercise in patients with moderately severe COPD. In addition previous studies have shown that interval training induces physiological adaptations in patients with COPD by allowing for higher work rates to be sustained during each training session with lower symptoms of dyspnea and leg discomfort compared to constant-load exercise.[25–27] The effectiveness of interval over constant-load training in COPD patients has been attributed to the fact that it is associated with reduced rates of exercise-induced dynamic hyperinflation and thus lower sensations of breathlessness during the training sessions.[19,25] Accordingly, the present investigation expands on those previous findings[19,25] by justifying the clinical utility of interval exercise training in COPD.

BODE index

In both groups the BODE index improved after the pulmonary rehabilitation programs. The improvement was significant for both interval-load training and constant-load training groups but not clinically meaningful as Cote et al.[5] defined as the minimum of 1.0 unit change in this index. In the study by Cote et al.[5] COPD patients participating in a multidimensional aerobic training program reduced the BODE index by (0.9 units). The difference between the study by Cote et al.[5] and the present study may be explained by the different level of disease severity and by the different structure of the exercise programs. To the best of the authors' knowledge, our study is the first to compare changes in the BODE index in terms of the two different types of exercise training. Taken together the data demonstrate that both training regimes help patients to shift to a lesser quartile of the BODE index. Interestingly

Table 2 Effects of training on BMI, MMRC, FEV_1% predicted, Wpeak, the 6-MWT, as well as dyspnea sensations, leg discomfort and SpO_2 recorded during the 6-MWT.

	CLT		ILT	
	Before	After	Before	After
BMI	24.6 ± 0.7	25.2 ± 0.6	25.5 ± 0.8	24.7 ± 0.7
MMRC	2.7 ± 0.2[a]	2.3 ± 0.2[b]	3.1 ± 0.2	2.7 ± 0.2[b]
FEV_1 (% predicted)	44.2 ± 4.2	44.2 ± 3.9	40.1 ± 3.9	41.4 ± 3.8
Wpeak (W)	51 ± 4	61 ± 5[b]	48 ± 4	62 ± 4[b]
6-MWT (m)	330 ± 20	374 ± 25[b]	333 ± 23	385 ± 22[b]
Dyspnea sensations	4.7 ± 0.4	4.5 ± 0.4	4.5 ± 0.5	4.2 ± 0.3
Leg discomfort	4.2 ± 0.7	4.0 ± 0.6	4.0 ± 0.3	4.3 ± 0.3
SpO_2 (%)	90 ± 1	91 ± 1	91 ± 1	92 ± 1

Dyspnea and leg discomfort were assessed by the modified Borg scale (1–10). SpO_2% was assessed at the end of the 6-MWT before and after the rehabilitation programs. MMRC and Wpeak were determined at the beginning and the end of the rehabilitation programs.
[a] Significant difference between ILT and CLT at $p < 0.01$.
[b] Significant differences within each group at $p < 0.01$.

the percentage of patients which reduced the BODE index by 1.0 unit was twice as high for the interval-load training compared to the constant-load training group. This is attributed to the tendency of interval-load training to improve the 6-MWT more than constant-load training.

Although neither interval-load training nor constant-load exercise improved the FEV_1 or the body mass index, both regimes significantly improved the Modified Medical Research Council dyspnea score. The magnitude of improvement is in agreement with the study by De Torres et al.[28] who compared the MMRC dyspnea score and the 6-MWT after pulmonary rehabilitation in patients with COPD.

6-min walking test

The 6-MWT is used for the evaluation of functional capacity in patients with COPD. The test is usually used in many cases of lung disability because it reflects the patients ability for daily activity.[4,5,29–32] The 6-MWT was standardized according to the ATS instructions because the encouragement of a patient can improve the test performance.[7] We decided to perform two 6-MWT efforts on two consecutive days in order to minimize the learning effect of the test. The second effort was on average 7 ± 2% better, possibly because of the improved patients' coordination, selection of pace and less anxiety for the test as previous studies have already described.[6,7]

In agreement with previous studies[26,29–32] the constant-load training group significantly improved the walking distance even though the improvement was not clinically meaningful as previous studies have defined a clinically

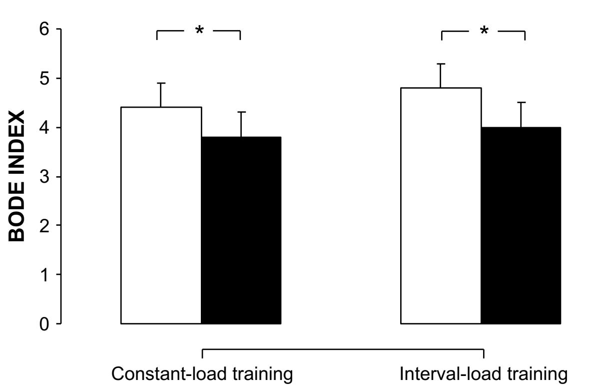

Figure 2 Effects of the two training regimes on the BODE index before (open bars) and after (closed bars) the rehabilitation program. Asterisks denote significant differences between pre- and post-training values.

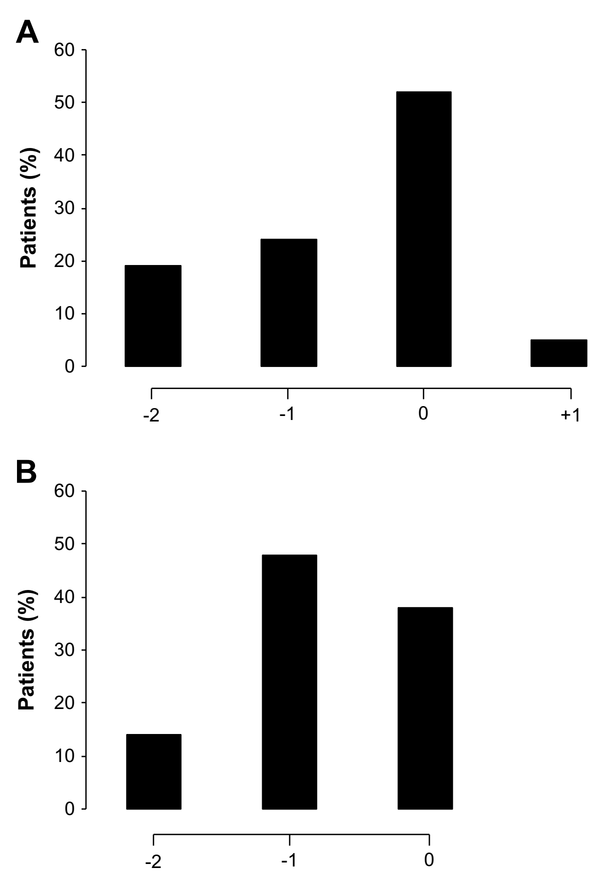

Figure 3 Fraction of patients experiencing different changes in units of the BODE index following completion of continuous (A) and interval (B) rehabilitative exercise training.

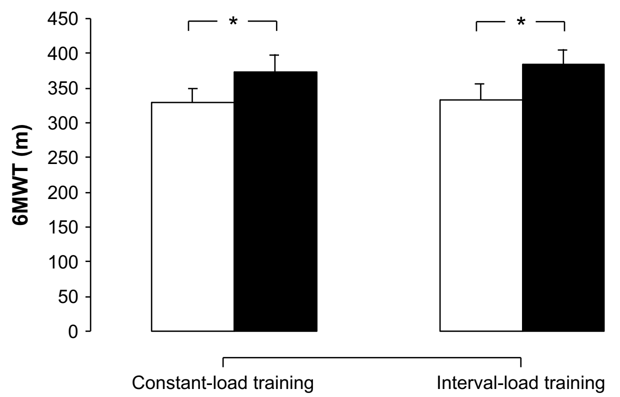

Figure 4 Effects of training in the 6-MWT before (open bars) and after (closed bars) the rehabilitation program. Asterisks denote significant differences ($p < 0.001$) between pre- and post-training.

meaningful change of 50–57 m.[33,34] The large variability between studies might be due to the difference in the structure of the training programs, the patients' degree of severity as well as the duration of the pulmonary program, hence direct comparisons between programs are difficult to be made.

On the other hand, the interval-load training group also improved the 6-MWT (by 52 ± 16 m) by an almost clinically meaningful margin.[33,34] Our findings expand those of previous studies which implemented interval training for patients with COPD in a pulmonary rehabilitation program albeit the degree of improvement in the 6-min walking distance was smaller in those studies.[16,27] The study of Gosseling et al.[16] was not randomized in terms of severity when patients assigned to interval-load training and constant-load training groups. In the study of Kaelin et al.[35] and Puhan et al.[27] the interval-load training group improved more the 6-min walking distance than the constant-load training group. This finding might be attributed to the different strategy of interval training adopted by Puhan et al.[27,36]

In the present study the difference in terms of clinically meaningful improvement in the 6-MWT between the two groups can be attributed to: a) the fact that interval-load training was sustained with lower symptoms of dyspnea and leg discomfort. This allowed patients to exercise with higher training loads. b) Interval-load training has the tendency to improve the muscle fiber morphological characteristics by a greater degree[20] c) interval-load training also tends to reduce ventilatory requirement and dyspnea sensation to a greater degree at an identical work rate during an incremental exercise test.[18,19]

In addition, at the end of the 6-min walking test post-training heart rate, SpO_2, symptoms of dyspnea and leg discomfort were similar to the pre-training values. This shows that both exercise training regimes induced significant physiological training effects. This is expected because exercise training improves the capacity of the heart to deliver blood to peripheral muscles and improves peripheral oxidative metabolism whish is associated with lower lactate and thus lower ventilatory drive and delayed onset of muscle fatigue.[11,18,19,37–39]

Cycle ergometry tolerance

The magnitude of improvement in peak work rate after the pulmonary rehabilitation programs was not different between the two groups. Such an improvement was significant for both groups and this finding is in agreement with previous studies,[14,15,35] which comprised interval- and constant-load training and with a meta-analysis[36] indicating that both modalities improved exercise capacity to a similar degree. This indicates that the short high-intensity stimuli, which are the strategy of interval-load training were equally effective in provoking the same improvement as the constant-load training.

There is a certain limitation of this study since the lack of simultaneous record of walking distance every minute during the 6-MWT (except at the end of the test) deprived us from having a more detailed insight into the assessment of the patients and to express changes in symptoms and heart rate relative to the actual distance travelled every minute. This point warrants more attention in the future.

In conclusion, the results of the present study show that interval-load training constitutes a good strategy for enhancing the BODE index and the functional capacity in patients with COPD. In addition, with interval training patients exercise more comfortably during each session with lower symptoms of dyspnea and leg discomfort. Therefore, interval exercise is highly recommended for the rehabilitation of the patients with COPD particularly those with profound muscle weakness and intense dyspnea sensations during exercise training.

Conflict of interest statement

The authors of the manuscript have not any conflict of interest to declare.

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